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REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-61 are currently pending, with claims 1-20 and 39-43 withdrawn from consideration as directed to a non-elected invention. Upon entry of this amendment, the amended and canceled claims are canceled and amended without prejudice or disclaimer. Claims 1-20 and 39-43 are canceled solely because they are directed to non-elected subject matter. Applicants reserve the right to reintroduce the unamended or canceled claims in this or another application. Claims 21-38 and 44-61 are thus pending following entry of this amendment.

II. Objections to the Specification

The title has been amended to be more descriptive of the currently claimed invention as requested.

III. Claim Rejections under 35 U.S.C. §112, Second Paragraph

Claims 26 and 46 are said to be unclear because the specification does not define what symptom to monitor. In response, it is submitted that those of ordinary skill know what symptoms are associated with a particular immune disorder. Moreover, the specification lists exemplary symptoms for a number of different immune diseases. For example, the specification describes symptoms for the following disorders: 1) endotoxin-induced septic shock (see, e.g., paragraph 75); 2) endotoxin-induced toxic shock (see, e.g., paragraph 78 and 79); 3) cell-mediated cytotoxicity immune disorders (see, e.g., paragraph 82); 4) graft-versus host disease (see, e.g., paragraphs 84 and 86); 5) asthma (see, e.g., paragraph 91); 6) delayed-type hypersensitivity reactions (see, e.g., paragraphs 94 and 97); 7) chronic immune disorders (see, e.g., paragraph 99); 8) granulomatis disease (see, e.g., paragraph 102); 9) Crohn's disease (see, e.g., paragraph 110); 10) ulcerative colitis (see, e.g., paragraph 111), 11) Grave's disease (see, e.g., paragraph 112); 12) Hashimoto's thyroiditis (see, e.g., paragraph 113); 13) systemic lupus erythematous (see, e.g., paragraph 114); 14) multiple sclerosis (see, e.g., paragraph 115); 15)

scleroderma (see, e.g., paragraph 116); 16) diabetes (see, e.g., paragraph 117); 17) uveitis (see, e.g., paragraph 118); 18) hepatitis (see, e.g., paragraph 119); and 19) psoriasis (see, e.g., paragraph 120).

These claims have also been amended to clarify that the symptom that is monitored is a symptom associated with the immune disorder that is being treated. This amendment is supported, for example, at paragraph 129. Claims 31 and 36 have been amended to address the antecedent basis concerns raised in the Office Action.

These amendments simply clarify these claims and do not narrow the claims. Accordingly, these claims are entitled to the same scope of equivalents as the original claims.

IV. Claim Rejections under 35 U.S.C. §112, Second Paragraph

Claims 21-38, 44-61 are rejected under 35 U.S.C. §112, second paragraph because the specification is said not to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation. The Office Action sets forth three major rationales to support this conclusion: 1) the specification only provides in vitro examples and not results from studies with animal model systems, thus the specification only enables claims to in vitro methods (see third paragraph on page 4 and first paragraph on page 5 of the Office Action); 2) the specification lacks adequate guidance on how to assess treatment efficacy (see, second paragraph of page 5 of the Office Action); and 3) for prophylactic treatment methods, the specification does not provide sufficient guidance on how to identify individuals at risk for an immune disorder (see, paragraph bridging pages 5 and 6 of the Office Action). Each of these issues will be addressed in turn.

With respect to the first rationale, the Office appears to take the position that the enablement requirement with respect to the present claims cannot be satisfied unless the specification provides examples with animal models that are supportive of the claims. Such a standard, however, is inappropriate for assessing enablement of the current claims.

The law is clear that in vivo examples are not required to enable treatment claims. Instead, in vitro examples are sufficient to constitute working examples, provided they reasonably "correlate" with the claimed method (see, e.g., MPEP 2164.02). An in vitro example

"correlates" with the claimed method if one skilled in the art would accept the in vitro example as reasonably correlating with the disease that the treatment methods are claimed to treat (Id.).

In evaluating whether there is a correlation, the law does NOT require a rigorous or an invariable exact correlation. The Federal Circuit has stated, for instance, that:

> [A] rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (*Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985); see also MPEP 2164.02.)

The Federal Circuit went on in the same case to conclude that often in vitro testing provides valuable predictive insight into the efficacy of in vivo results and that typically there is a reasonable correlation between the two, stating:

> *[I]n vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween.* Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. Iizuka has not urged, and rightly so, that there is an invariable exact correlation between in vitro test results and in vivo test results. Rather, Iizuka's position is that successful in vitro testing for a particular pharmacological activity establishes a significant probability that in vivo testing for this particular pharmacological activity will be successful. (*Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), emphasis added.)

These statements from the Federal Circuit thus demonstrate two points: 1) that in vitro examples can be used as predictors of in vivo efficacy, and 2) that in vitro results need not establish an exact correlation between the proposed treatment and the disease being treated for

the results to be predictive of in vivo utility. Instead, the results only need demonstrate a *reasonable* correlation.

So the broad conclusion in the Office Action on page 4, third paragraph that "[s]ince there is no animal model system in the specification to treat an immune disorder, . . . it is unpredictable how to correlate test tube results with in vivo studies" is inconsistent with the foregoing statements from the Federal Circuit. As just noted, the court stated that in vitro results can, in fact, often be predictive of in vivo results. Moreover, although the Office Action appears to require an exact correlation between the claims and the experimental results, the court makes clear that this is not a requirement.

In view of the foregoing statements, the enablement inquiry thus does not depend solely on whether the specification provides in vivo examples as the Office Action appears to imply. Rather the correct inquiry is whether one of ordinary skill in the art could *reasonably* consider the in vitro examples that are presented in the specification to correlate with treatment of an immune disorder. It is submitted that the answer to this inquiry is "yes."

The in vitro results correlate with the claimed methods because the numerous examples presented in the application demonstrate that treatment of various immune cells with rhesus CMV IL-10 resulted in a decrease in the concentration of molecules (e.g., various cytokines and Class I and Class II MHC proteins) known to be causative agents of immune disorders and resulted in an increase in the concentration of molecules (e.g., HLA-G) known to protect against immune disorders.

The following chart summarizes the results of studies conducted with rhesus CMV IL-10 that specifically illustrate this correlation:

Example	Molecule	Correlation between Molecule and Immune Disorder
4	IFN-γ	Paragraphs 88, 94, 97, 99 and 104 note that IFN-γ is a causative factor associated with hypersensitive immune disorders, delayed type hypersensitivity disorders and chronic immune disorders like chronic inflammation. Example 4 demonstrates that treatment of human

		peripheral blood mononuclear cells (PBMCs) with rhesus CMV IL-10 inhibited IFN-γ synthesis, indicating that treatment with rhesus CMV IL-10 would protect against these disorders.
6 and 8	TNF-α	Paragraphs 74, 88, 99 and 104 indicate that TNF-α is involved in endotoxin-induced septic shock, hypersensitive immune disorders, chronic immune disorders and inflammatory disease. Examples 6 and 8 demonstrate that treatment of human PBMCs and monocytes with rhesus CMV IL-10 inhibited TNF-α synthesis, indicating that treatment with rhesus CMV IL-10 would protect against these disorders.
10	GM-CSF	Paragraphs 88 and 95 describe the involvement of GM-CSF in hypersensitive immune disorders, and pathogen-induced delayed type hypersensitivity reactions. Example 10 shows that treatment of human monocytes with rhesus CMV IL-10 inhibited GM-CSF, thereby indicating that treatment with rhesus CMV IL-10 would protect against these disorders.
12	IL-1α	Paragraph 74 discusses, for instance, the association between IL-1α and endotoxin induced septic shock. Example 12 demonstrates that treatment of human monocytes with rhesus CMV IL-10 inhibited IL-1α, indicating that treatment with rhesus CMV IL-10 would protect against this disorder.
14	IL-6	Paragraph 88 notes that IL-6 is correlated with hypersensitive immune disorders, for example. Example 14 shows that treatment of human monocytes with rhesus CMV IL-10 inhibited the synthesis of IL-6, indicating that treatment with rhesus CMV IL-10 would protect against these disorders.
15 and 16	Classical Class I and	These molecules are involved in eliciting immune activation (see, e.g., paragraph 28). Examples 14 and 15 illustrate that treatment of

	II MHC Molecules	human monocytes with rhesus CMV IL-10 reduces the surface expression of these molecules, thus indicating that such a treatment would protect against immune disorders.
17	HLA-G, a Nonclassical Class I MHC Molecule	*Increased* expression of this molecule is associated with decreased immune activation and hence a decreased risk of immune disorders. Example 17 shows that HLA-G surface expression on human monocytes was *increased* upon treatment with rhesus CMV IL-10, indicating that such a treatment protects against immune disorders.

It is submitted that this extensive evidence more than satisfies the requirement that the examples provide sufficient information such that one of ordinary skill could *reasonably* conclude that a correlation exists between the claimed methods and the study results. The burden is on the Office to explain why these numerous examples do not correlate with the current claims (see MPEP 2164.02).

With regard to the second concern expressed in the Office Action, Applicants disagree with the assertion that the specification provides insufficient teaching to enable one of ordinary skill to determine whether a treatment has been effective. Applicants disagree because, to reiterate a point made above, symptoms associated with various immune diseases are known in the art. Furthermore, the specification provides considerable detail on specific symptoms that are associated with a large number of diverse immune disorders (see sections of specification referred to above in Section III). One of skill would know that one option for monitoring the effectiveness of a treatment would be to monitor whether the treatment ameliorated one or more of the symptoms associated with the particular disease being treated.

With respect to the third concern, Applicants also respectfully disagree that the claims are not enabled because they encompass prophylactic methods. The Office Action takes the position that one skilled in the art would not know how to identify appropriate individuals for prophylactic treatment nor know how to determine if the treatment had been effective.

In response, it is submitted that those of ordinary skill in the art could readily identify individuals that could benefit from prophylactic treatment for a number of different

immune disorders and ascertain the efficacy of the treatment based upon general knowledge in the art. For example, individuals susceptible to a number of immune disorders can be identified based upon upcoming events in the individual's life that put them at risk (e.g., a medical procedure), past events that put the individual at risk (known exposure to a pathogen which can induce an immune disorder in an infected individual), genetic susceptibility, clinical history and risk factors associated with life style. Monitoring the efficacy of treatment can also be straightforward in a number of treatments. For instance, by monitoring various symptoms known to be associated with the disorder (see Section III above).

The following list summarizes examples of approaches that can be taken with a variety of different diseases. This list is only exemplary; similar approaches could be taken for a number of other disorders.

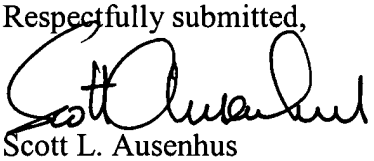
Disease	Identification	Assessment of Efficacy
Graft-versus-host disease	A person that is about to undergo, or has recently undergone, a grafting procedure or is at risk for rejection.	Determine using standard medical evaluation whether there is rejection of the graft
Hepatitis	A person that has cirrhosis of the liver or antibody positivity for hepatitis virus	Monitor liver enzymes, assessment of jaundice, enlarged liver, bilirubin levels
Endotoxic Shock/Sepsis	An individual that has been exposed to hospital pathogens or that has a disseminated bacterial infection	Blood interferon gamma levels, fever, cardiovascular distress, tachypnoea
Delayed Type Hypersensitivity Reactions	As indicated in the specification, these diseases can be caused by various microbial infections (see, e.g., paragraphs 94 and 95). Detection of such infections via standard medical means can be used as a screening	Reduction in rash or swelling.

	method. Administration of CMV IL-10 to an infected person is still a prophylactic treatment because the onset of the disease is delayed. Treatment may also be indicated in cases of contact induced DTH eg poison ivy/oak, turpentine etc.	

So for all the foregoing reasons, it is submitted that the pending claims are enabled and that this rejection should be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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